Support for the above amendments can be found throughout the specification as originally-filed. More specifically, exemplary support for the amended claims may be found at pages 4-6, 24-27, 29-31, and 33-34 of the instant specification. The amendment to claim 15 is formalistic in nature and the amendment to claim 2 is purely for grammatical reasons. Accordingly these amendments raise no issues and raise no new matter.

The issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

1. Applicants acknowledge with appreciation the withdrawal of the rejection of claims 1-2, 4, 6-8, and 14-22 under 35 U.S.C. 102(b) as being anticipated by Young (US Patent 5,698,198); the rejection of claims 3 and 5 under 35 USC 103(a) as being unpatentable over Young (US Patent 5,698,198) in view of Richards (US Patent 5,043,267); and rejection of claims 1-8 and 14-18 under 35 USC 112, second paragraph.

2. Claims 1-8 and 14-18 are rejected under 35 U.S.C. 112, first paragraph, because allegedly "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims." [Office Action at page 3, lines 21-23]. In particular, the Examiner asserts that "the claims are rejected because the method does not recite positive steps necessary to determine whether binding has occurred . . ." [Office Action at page 4, lines 5-6]. The Examiner goes on to state that "the specification appears to make the conclusion that detectable labels are required to determine binding and/or presence of a bacterial antigen. Therefore, the Examiner contends that the claims are only enabled for the use of detectably labeled binding agents." [Office Action at paragraph bridging pages 4-5]. Applicants respectfully traverse this rejection.

In contrast to the Examiner's assertion, the specification provides a number of examples teaching the skilled artisan how to determine whether binding has occurred. For example, Applicants respectfully submit that in the paragraph bridging pages 33-34, the specification recites the various means for detecting binding including a lateral flow assay, ELISA, RIA (radioimmunoassay in which unlabeled antibodies form a visible ring in the agar when complexed to its specific antigen), FACScan analysis, and agglutination assays etc. to name just

a few methods. Furthermore, in Example III and in Figures 4A-4D, the specification elaborates on the agglutination assays and teaches that, a visible cross-linked matrix is formed when the antibodies on latex beads cross-link clinically relevant amounts of bacterial cells in a biological sample. Accordingly, it is Applicant's position that the specification teaches both methods where the agents are detectably labeled and methods where the binding agents are not detectably labeled, i.e., the specification enables the full-breadth of the claimed invention.

In view of the telephonic interview, the claims have been amended to recite "detecting binding" instead of "determining binding." This amended has been made merely to expedite prosecution and does not alter the scope of the claimed invention. In view of the above remarks and amendments, Applicants respectfully request withdrawal of this rejection.

3. Claim 18 is rejected under 35 USC 112, second paragraph, allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, the Examiner asserts that although the preamble is drawn to screening gram-negative bacteria, the determining step recites gram-negative and gram-positive bacteria.

Applicants have amended claim 18 to remove the step of determining gram-positive bacteria, thereby obviating the ground of the rejection.

4. Claims 1, 3-6, 14, and 16 are asserted as allegedly being unpatentable under 35 USC 103(a) over Chan (EP 461,462) in view of McLaughlin (U.S. Patent 4, 683,196) and Tadler *et al.* (*J. Clin. Lab. Anal.* 3: 21-25 (1989)). Specifically, the Examiner contends that:

> [I]t would have been prima facie obvious to modify the simultaneous multiple analyte detection immunoassay taught by Chan by incorporating a set of binding agents taught by McLaughlin and Tadler et al., since McLaughlin teach antibodies which specifically bind to gram-negative bacteria in order to determine their presence and/or absence while Tadler et al. teach well known binding agents that binds lipotechoic acid of gram-positive bacteria.

See [Office Action at page 3, lines 21-23]. Applicants respectfully traverse this rejection. First, the primary reference Chan teaches an immunoassay to detect the presence or amount of at least one antigen which may be present in a test sample by contacting the test sample with a

solid support on which one or more antibodies are immobilized as discrete test sites, and detecting the antigen-antibody complexes formed on the solid support. In other words, Chan conducts multiple discrete tests against multiple analytes wherein different antibodies to different antigens are singly put in discrete wells of a microtiter plate and wherein the entire plate is read simultaneously by an assay device. By contrast, the claimed invention is directed to one test which indicates the presence of multiple analytes using a set of binding agents to different antigens within the same microtiter well.

Further, the only antigens identified by Chan are HIV-1, HIV-2, and HCV (see page 4, lines 27-28), wherein different viral antigens are detected at discrete test sites; there is no teaching or suggestion of the detection of an entire class of bacteria using a pan-generic binding agents. In addition, Chan does not teach or suggest that the assay could be used to detect a clinically relevant amount of bacteria from the blood or blood products as claimed herein. Moreover, the detection system taught by Chan is drawn to the detection of known antigens and not to the detection of a number of unknown antigens in a single screening. In brief, there is no teaching of a discrete test that allows detection an entire class of microorganisms using a pan-generic set of binding agents. Thus, Chan fails to disclose, suggest, or teach, the immunoassay as claimed herein.

The Examiner looks to McLaughlin and Tadler et al. to cure the deficiencies of the primary reference. McLaughlin (U.S. Patent 4,683,196) is cited as teaching methods and materials for the identification of lipopolysaccharide (LPS) producing microorganisms which share a conserved region in the middle of the protein. And, Tadler et al. is cited as teaching a sandwich immunoassay used to detect LTA, which is a major cell wall constituent of gram-positive bacteria form whole blood.

Applicants respectfully submit that the secondary references fail to cure the deficiencies of the primary references. In fact, a close review of Tadler et al. shows that this document teaches away from the claimed invention. Specifically, at page 24, right column at the 2nd full paragraph of Tadler et al. teach that "although the present assay has good sensitivity, *it is not adequate to detect most bacteremias.* A 2-3 log increase in assay sensitivity would be required to achieve the ability to rapidly detect gram positive bacteremia." Additionally, Applicants note that in Table 1, not all of the antibodies were able to detect all of the gram-positive bacteria,

indicating that they cannot recognize an entire class of microorganisms. Consequently, Tadler et al. do not teach a blanket screening assay that can detect most bacteremias, or even all gram-positive bacteria. In fact, as stated above Tadler et al. *teaches away* from the instant claimed invention because one of ordinary skill would not use the binding agents disclosed by Tadler et al. to develop a safe and effective blood screening assay.

Secondly, Applicants respectfully submit that to sustain a rejection under 35 U.S.C. § 103, two basic criteria must be established. First, there must be a suggestion or motivation to modify the teachings of the primary reference (Chan), or to combine it with the teachings of other references, to arrive at the claimed method. Second, there must be a reasonable expectation that such a combination would be successful. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the instant disclosure. See, In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). See also MPEP 2143.03.

In this case, the prior art fails to suggest the instant combination and indicates that a skilled artisan would not have expected that an immunoassay as claimed herein would be effective in screening blood and blood products for clinically relevant amounts of bacteria. The references cited in this rejection were published in 1987, 1989, and 1991. If, as the Examiner suggests, such a procedure had been easy to make, given the critical need for such screening methodologies in blood banks (which currently dispose of blood after a defined period of time rather than test for bacteria), and given that more than a decade has passed since these prior art references were made available to the skilled artisan, such a screening assay would have been developed prior to the filing of the instant invention.

The state of the art at the time of filing may be summarized by the teachings set forth in Wagner, S.J., *Int. J. Med. Microbiol. Virol. Parasitol. Infect. Dis.* 283(3): 253-257. Wagner discloses that there was a critical need in the art for such a blood test, and that every attempt to produce such an immunoassay had failed. Wagner, S.J. stated that as late as 1996, that "no common antigenic source exists for broad-based bacterial detection". Accordingly, it appears highly unlikely that at the time of filing of the instant application, the skilled artisan would have

been motivated to develop such an immunoassay, because, the popular belief was that such assays would not to be effective.

Both the critical need for such a test and the lack of a reasonable expectation of success that assays as claimed herein would be effective are further set forth in the citations discussed herein:

(1) In an on-line publication (www.jhita.org/023099.htm 1/6/2000) testimony was provided by Jane Henney, FDA's commissioner to the U.S. House of Representatives hearing on February 23, 1999 on issues of blood safety: "The safety and adequacy of the blood supply and blood products is one of the highest priorities of the FDA and the Department of Health and Human Resources." (Bottom of page 1) ["The technology associated with disease detection in blood donors is continually improving, but risks remain.] For a number of serious and life-threatening infections, there is a limited period after a possible donor has been infected, which the infection is not detectable by available methods. ... The risk to patients from bacterial contamination of blood and from blood band error must also be reduced."

(2) Goldman and Blajchman (Transfusion Medicine Review 1991; Vol. V, No. 1: 73-83) teach that in there are several difficulties involved in the bacteriologic screening of blood products. Traditional culture techniques require a lengthy incubation period of several days. False positives may occur because of contamination during the innoculation procedure itself. False negatives may occur because of the low numbers of bacteria present and suboptimal media or incubation temperatures for a given organism (see bottom of right column of page 80 to top of page 81).

(3) P. Ann Hoppe (Transfusion 1992; 32(3): 199-201) teaches that although numerous studies have been performed by the FDA and others, no rapid and reliable tests exist that could be readily applied in the blood bank setting (see bottom of right column of page 199). The prospect of using a simple color comparison to detect bacterial contamination remains problematic, and the search for alternative procedures for detecting contaminating bacteria should continue. ... While there is promise in the observations of Kim et al., it is premature to conclude that this procedure will provide another increment in the safety of blood used for transfusions (see final paragraph on page 201).

(4) Bjajchman et al. (Transfusion 1994; 34(11): 940-942) teaches that transfusion-associated bacterial sepsis has again begun to be recognized as a problem for blood component recipients. ... The recent steep increase in the number of reports of sepsis due to the transfusion of infected blood components has involved both red cell and platelet transfusions (see left column of page 940). [R]outine random-donor PC units prepared ... showed that approximately 1 in 1,000 units was contaminated with bacteria. [T]ransfusion-associated bacteremia is the most common transfusion-related infection currently confronting the transfusion medicine community (see top of left column on page 941). Effective methods for bacteriologic monitoring, using appropriately evidence-based studies, would have to be developed (see paragraph 2, right column of page 941).

(5) Roger Svoboda and Karen Lipton (AABB Association Bulletin #96-6, dated August 7, 1996) disclose that to date, there has been no surveillance system or epidemiologic study to assess the risk of bacterial contamination of blood and blood components in the United States (see section 1). Part of the difference in the number of estimated versus reported deaths is most likely due to the lack of a standardized approach to evaluating instances of suspected transfusion-associated sepsis (see section 2). The overall frequency of septic complications resulting from bacterial contamination varies widely between institutions and may be due to variability in identification and reporting, or may reflect true variations incidence (see section 4). At present, there is no fully satisfactory method for such monitoring (see section 2, second sentence). Subsections a-c describe the disadvantages associated with each testing technique – e.g., not sensitive enough, too expensive, no clear end-point for a negative finding, not yet validated. Major emphasis should be given to developing and evaluating practical, sensitive and specific screening assays for the detection of bacteria in platelet concentrates and to developing methods to decontaminate cellular blood components (see section 7a).

(6) Klein et al. (Transfusion 1997, 37: 95-101) discloses a summary of the September 27, 1995, conference on the microbial contamination of blood components was held at the Warren G. Magnuson Clinical Center of the National Institutes of Health. Dr. Cookson indicated that screening questions aimed at eliminating symptomatic donors would not be specific enough to prove effective at preventing use of bacterially contaminated blood (see top of right column, page 96). Methods that have a high rate of false-positive results would have limited practicality

for blood component screening. To be cost effective for blood bank indications, the optimal test would have to be simple enough to be performed in a transfusion service or blood center. Sampling difficulties that can result in false-positive tests and the difficulty of assigning an exact quantity for all bacteria in order to define the acceptable level of sensitivity for detection systems. Although five cases of sepsis were prevented, some cases were missed and a number of false-positive results were reports (see page 97). The test procedure using an RNA probe was to cumbersome for routine blood bank screening and its use is no longer being pursued by the manufacturer. Visual inspection of PCs by the swirl test did not prove useful for detecting bacterial contamination. Glucose testing was not found to be a viable alternative (see page 98). WBC reduction had no impact on bacterial growth. Further, it is not predictable as to which species of bacteria would be affected by WBC reduction. Filtration had no impact on the bacterial levels – in no case were the bacteria eliminated, and in fact, bacteria reached the same titer at the stationary phase of growth, whether or not the pool was filtered (see page 99). A reduction in storage time would be acceptable only if the current processing time were materially decreased; such an outcome does not appear to be possible (see right column of page 100). Dr. Sayers called for further investigation into novel screening and detection methods, especially because the conference suggested that chemiluminescence, once thought promising, is no longer being pursued for this purpose.

(7) Stephen Wagner, (*Int. J. Med. Microbiol. Virol. Parasitol. Infect. Dis.* 283(3): 253-257) teaches that no practical test is available for bacteria detection in donor blood. Development of a bacterial test will be a formidable task, and will not likely parallel the antibody-based tests frequently used for detection of viral infections (see page 253). Unfortunately, it is difficult to estimate what level of bacteria constitutes dangerously high levels because so few blood units have been quantitatively titered that have been associate with septic events. (see page 254, first paragraph). None of the methods for detecting bacterial contamination are feasible for immediate implementation (see page 255). Detection of bacterial antigens represent an interesting potential method. One difficulty of developing immunological-based tests is that there are likely to be no common antigens on the surface of the diverse species that have been implicated in transfusion-associated sepsis. No practical methods are available for detecting bacteria which can routinely implemented. One of the problems in reducing

Claim object the method either detects or doesn't detect bacteria

transfusion-associated bacterial sepsis is that a broad range of species with vastly different surface properties may be present (page 256).

(8) Barrett et al. (Transfusion 1993; 33(3): 228-233) disclose that bacterial contamination can result in adverse clinical sequelae in transfusion recipients and that both culturing and Gram staining are poor methods of screening for contaminated units. More sensitive and specific methods of generalized screening for bacterial contamination are needed (see abstract).

(9) Jacobs et al. (Transfusion 2001; 41: 1331-1334) teach that transfusion of bacterially contaminated blood components, especially platelets, is an ongoing problem with variable clinical sequelae, including serious morbidity and mortality. Unfortunately, most of the detection methods are too insensitive, as well as having many other limitations. Even microbiologic culture would not guarantee detection of all contaminated units, because of variability in the inoculum, in the kinetics of bacteria growth, and in the length of the lag phase (see page 1332). In an era in which the risk of transmission of many blood-borne viruses, particularly HIV, has virtually been eliminated, it is paradoxical that the earliest recognized infectious transfusion complication, bacterial contamination, is now the most frequent and is providing the most difficult to eradicate (see page 1333).

(10) Wagner and Robinette (Transfusion 1998; 38: 674-679) teach that despite new measures using plastic containers, transfusion-associated bacterial sepsis continues to be a concern in transfusion medicine. Septic deaths, although infrequent, have been a recurrent theme in the literature during the last 30 years (see page 674). Despite many attempts, no detection technique has been developed that meets all the requirements for a successful test. The automated system of the invention disclosed in the paper was unable to predict the presence of organisms in contaminated PCs in some experiments (see page 677). Another issue of concern is the frequency of false-positive units that might be unnecessarily destroyed.

Applicants respectfully submit that these documents clearly show that the requirements under 35 U.S.C. 103(a) of a reasonable expectation of success cannot be satisfied. Further, see MPEP 716.01(a) Objective Evidence of Nonobviousness. The MPEP states that "[a]t the pinnacle of evidence of skepticism, though not required for finding a lack of reasonable expectation of success, is evidence in the prior art that teaches away from the claimed

invention." A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path taken by the applicant". In re Gurley, 27 F.3d 551 (Fed. Cir. 1994). The Tadler et al. reference in conjunction with the state of the art as exemplified by the documents cited above clearly teach away from the claimed invention.

Third, the courts have consistently held that "obvious to try" is not to be equated to obviousness under 35 USC 103. In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988); and Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367 (Fed. Cir. 1986). An "obvious to try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 902 F.2d 943 (Fed. Cir. 1990). Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. See Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448 (Fed. Cir. 1985). A finding to the contrary represents impermissible use of hindsight, e.g., using the inventor's success as evidence that the success would have been expected. See In re Kotzab, 217 F.3d 1365 (Fed. Cir. 2000). In this case, the combination of Chan, McLaughlin, and Tadler et al., exemplify an "obvious to try" situation.

The Office Action further states that the recitation of a method of screening of blood from a donor mammal for transfer to a recipient mammal, has not been given patentable weight because the recitation occurs in the preamble. In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951) are cited as giving weight to this line of reasoning.

Applicants respectfully disagree. Both, In re Hirao and Kropa v. Robie, involved composition claims and were drawn a new intended use of an old compound. Here, in contrast, we have method claims. The Federal Circuit decided on April 2, 2002 (285 F.3d 1029) that

when an intended use is recited in the preamble of a *method* claim, and a "wherein" clause is part of the body of the claim that reads back on the preamble, the preamble of the method claim should be given patentable weight. Therefore, in this case, Applicants assert that the recitation of the "transfer to a recipient mammal" in the preamble should be given patentable weight in the claim as drafted.

To conclude, Applicants respectfully submit that the above rejection fails to establish a prima facie case of obviousness. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

5. Claims 2 and 15 are asserted as allegedly being unpatentable over Chan (EP 461,462), McLaughlin (U.S. Patent 4, 683,196) and Tadler et al. (*J. Clin. Lab. Anal.* 3: 21-25 (1989)), as applied to claims 1 and 14 above, and further in view of Chang et al. (U.S. Patent 5,200,323) under 35 U.S.C. 103(a). The rejection sets forth that Chan, McLaughlin, and Tadler et al do not teach that in the absence of a clinically relative amount of bacteria is transferred to a recipient mammal. However, the Examiner asserts that Chang et al. (U.S. Patent 5,200,323;"the '323 patent") cures the deficiencies of the primary references (Column 1 lines 8-10, column 2 lines 31-33, and column 4 lines 10-30). Applicants respectfully traverse this rejection.

Applicant's position regarding the Chan, McLaughlin, and Tadler et al. references has been stated *supra*. Applicant assert that the entire '323 patent is directed to the safety of transfer of modified hemoglobin blood substitutes (see column 4 at lines 10-30), not a method of screening blood/blood product for bacteria and found to be free of gram positive and gram negative bacteria for transfusions, nor is it even directed to the detection of bacteria at all.

The '323 patent specifically teaches that donor blood (RBC) can be in short supply, especially in major disaster situation or during war, transfusions require cross-matching, have a short storage time unless they are stored by some expensive and complex means. As a result, focused on the potential uses of hemoglobin extracted from red blood cells – therefore, hemoglobin must be modified before it can be used as a blood product. Two major groups of modified hemoglobin are – (1) encapsulated (2) cross-linked. (See column 2, lines 42-65).

Any and all screening contemplated in the '323 patent is drawn to the screening for the safety of the modified human hemoglobin products (see column 3 and the claims), not for bacterial antigens.

Therefore, the '323 patent does not make up the deficiencies of the Chan, McLaughlin, and Tadler et al. references, each of which have their own deficiencies as described *supra*.

6. Claim 7 is asserted as allegedly being unpatentable over Chan (EP 461,462) in view of Tadler et al. (*J. of Clin. Lab. Anal.* 1989; 3: 21-25) under 35 USC 103(a). Applicants respectfully traverse this rejection.

The Examiner's position and Applicant's rebuttal with respect to the Chan and Tadler et al. references have been discussed *supra*. Applicants note that instead of the teachings of the Tadler et al. reference, the examiner repeats the teachings of the McLaughlin (U.S. Patent 4,683,196), which is drawn to gram-negative bacteria, not Gram-positive bacteria.

Regardless, the deficiencies of the Chan, McLaughlin, and Tadler et al. have been described *supra*. Applicants respectfully request withdrawal of the rejection based on the arguments set forth herein.

7. Claims 8 and 18 are asserted as being unpatentable over Chan (EP 461,462) in view of McLaughlin (U.S. Patent 4,683,196) under 35 USC 103(a). Applicants respectfully traverse this rejection.

The Examiner's position and Applicant's rebuttal with respect to the Chan and McLaughlin references have been discussed *supra*.

Applicants assert that the requirements of 35 USC 103(a) with the Graham v. Deere factors have not been met and respectfully request withdrawal of the rejection based on the arguments set forth *supra*.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: October 8, 2002

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